

Acute myeloid leukaemia therapeutic innovation and clinical trials

Craddock, Charles

DOI:

[10.1111/bjh.17146](https://doi.org/10.1111/bjh.17146)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Craddock, C 2020, 'Acute myeloid leukaemia therapeutic innovation and clinical trials: past, present and future', *British Journal of Haematology*, vol. 191, no. 4, pp. 568-572. <https://doi.org/10.1111/bjh.17146>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

NOW GRANTED EU CONDITIONAL MARKETING AUTHORISATION.*
TECARTUS ▼ (AUTOLOGOUS ANTI-CD19-TRANSDUCED CD3+ CELLS)

IS INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)
 AFTER TWO OR MORE LINES OF SYSTEMIC THERAPY INCLUDING A BRUTON'S TYROSINE KINASE (BTK) INHIBITOR¹

PRESCRIBING INFORMATION

**PATIENTS WITH MCL
 POST-BTK INHIBITOR
 FAILURE FACE
 POOR PROGNOSSES²⁻⁴**

**REGAIN CONTROL
 WITH AN ORR OF
 93% WITH TECARTUS²**

(PRIMARY ENDPOINT, IN THE PRIMARY ANALYSIS SET (N=60)²)



Kaplan-Meier estimate of the duration of response, as assessed on the basis of review by the independent radiologic review committee, among 56 patients in the primary efficacy analysis who had an objective response. Tick marks indicate censored data.²
 Adapted from Wang M, et al. *N Engl J Med*. 2020.

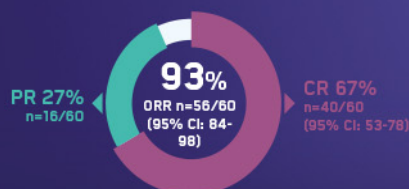
Not an actual patient.

**IN THE PRIMARY ANALYSIS SET
 (N=60) AT 12.3 MONTHS:²**

EFFECTIVE²

PRIMARY ENDPOINT:

PERCENTAGE OF PATIENTS WITH AN OBJECTIVE RESPONSE (CR OR PR)²



DURABLE

SECONDARY ENDPOINT: DOR²

The median duration of response was not reached (95% CI: 8.6-NE) at a median follow-up of 12.3 months in the primary efficacy analysis set²

- In the patients with ≥2 years follow-up, 43% (N=12/28) remained in remission²

TOLERABILITY

Tecartus led to serious and life-threatening toxic events of the type reported with other anti-CD19 CAR T-cell therapies.² The most significant and frequently occurring adverse reactions were cytokine release syndrome (91%), infections (56%) and encephalopathy (51%)¹

RAPID

Median time to response was 1 month in the primary analysis set² (range: 0.8-3.1)²

Regain control with Tecartus at www.kitecartforum.co.uk (This website contains promotional content)

ZUMA-2 was a phase 2, single-arm, open-label, multicentre trial evaluating the efficacy and safety of a single infusion of Tecartus in adult patients with R/R MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi (ibrutinib or acalabrutinib).²

*Patients are expected to enroll in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.¹

¹The first 60 patients treated with Tecartus who had 7 months follow-up.²

BTKi=Bruton's tyrosine kinase inhibitor; CAR=chimeric antigen receptor; CI=confidence interval; CR=complete response; DOR=duration of response; MCL=mantle cell lymphoma; NE=could not be estimated; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory.

REFERENCES: 1. Tecartus. Summary of Product Characteristics. 2. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle cell lymphoma. *N Engl J Med*. 2020;384(14):1331-1342. 3. Smith A, Roman E, Appleton S, et al. Impact of novel therapies for mantle cell lymphoma in the real world setting: a report from the UK's Haematological Malignancy Network (HMRN). *Br J Haematol*. 2018;181(215-228). 4. Smith A, Roman E, Appleton S, et al. Impact of novel therapies for mantle cell lymphoma in the real world setting: a report from the UK's Haematological Malignancy Network (HMRN) - supplementary appendix. *Br J Haematol*. 2018;181(215-228).


Tecartus, the Tecartus Logo, XLP, KITE KONNECT, the KITE KONNECT Logo, KITE, and the KITE Logo are trademarks of Kite Pharma, Inc. GILEAD is a trademark of Gilead Sciences, Inc. All other trademarks referenced herein are the property of their respective owners.

TECARTUS ▼
 (autologous anti-CD19-transduced CD3+ cells)
 dispersion for infusion

© 2020 Kite Pharma, Inc. All rights reserved.
 UK-CTH-2021-01-0015.
 Date of preparation: February 2021



Acute myeloid leukaemia therapeutic innovation and clinical trials: past, present and future

Charles Craddock^{1,2} 

¹Centre for Clinical Haematology, Queen Elizabeth Hospital, and ²CRUK Cancer Trials Unit, University of Birmingham, Edgbaston, Birmingham, UK

Summary

Outcomes in acute myeloid leukaemia have improved steadily over the last six decades thanks to advances in disease classification, risk stratification and the advent of new drug and transplant therapies. Over this period the UK has made a major contribution to this international effort, both through its delivery of large prospective randomised trials with integrated genomic and measurable residual disease assessments and its pioneering role in the development of allogeneic stem cell transplantation as a potent anti-leukaemic therapy.

Keywords: AML, therapeutic innovation, clinical trials.

**'This royal throne of kings, this sceptred isle...
This blessed plot, this earth, this realm...':
Richard II**

The UK's contribution to the improvement of outcomes in adults with acute myeloid leukaemia (AML) is a tribute to the work of many clinicians and translational scientists. However, three figures stand out in the UK's international contribution to advancing the treatment of AML. None more so than Alan Burnett. Combining an exceptional ability to identify tractable therapeutic questions and a visionary recognition of the power of randomised trials in haematological malignancies Alan's ability to integrate large and small hospitals across the UK into a cohesive trials network resulted in the seamless delivery of a pipeline of practice informing trials and has served as a model for other diseases. At the same time, by making trial entry the default option in hospitals across the length and breadth of the land, he was responsible for the standardisation of routine care in AML to substantial

patient benefit. A common theme championed by Sir John Bell in the HM Government Life Sciences Strategy is the UK's opportunity to leverage the combined strengths of its world class science base and the internationally significant cohorts resident within the NHS to accelerate the delivery of clinical trials with embedded discovery medicine. There can be no better exemplar of the UK's potential to excel as a uniquely effective international destination for clinical trial delivery than the cohort of AML trials delivered by Alan, sometimes with ruthless Glaswegian efficiency, which have transformed treatment paradigms consequent upon the integration of disease biology and measurable residual disease (MRD) quantitation into routine trial design.

John Goldman played a central role in the management of myeloid leukaemias internationally and serves as an abiding inspiration to so many colleagues fortunate enough to work with him. John was the embodiment of the clinician scientist combining a fascination with disease biology, specifically the molecular pathogenesis of chronic myeloid leukaemia (CML), coupled with a relentless spirit of therapeutic innovation. Over and above his enormous contribution to the transformation of outcomes for patients with CML, John's work also laid the ground for many of the recent pivotal advances in the management of AML. His effective partnership with Brian Druker in the development of imatinib mesylate was critical to the subsequent development of targeted therapies in AML. John also pioneered the use of quantitation of *BCR-ABL* transcripts numbers in the assessment of response to drugs and transplant; work that informed the development of MRD strategies in AML. Finally John played a central international role in the development of allogeneic stem cell transplantation (allo-SCT) as a curative therapy in myeloid malignancies and his work underpins the central role allografting now plays in the management of high-risk AML. More than anything however, it was John's warmth, generosity, profoundly liberal instincts and passionate belief in collaboration with European and international colleagues that inspired generations of haematologists. And the unforgettable ward rounds during which the works of Shakespeare-especially his favourite play *Richard II* were as much a topic of conversation as the

Correspondence: Professor Charles Craddock, Centre for Clinical Haematology, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom.
E-mail: charles.craddock@uhb.nhs.uk

First published online 13 November 2020 © 2020 The Authors. *British Journal of Haematology* published by British Society for Haematology and John Wiley & Sons Ltd *British Journal of Haematology*, 2020, **191**, 568–572
doi: 10.1111/bjh.17146

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

relayed opinions of his dear friend and brilliant colleague Robert Peter Gale, all the way from the unspeakably glamorous Los Angeles, on the management of a particularly challenging patient.

My other personal inspiration has been David Grimwade, a brilliant, generous and innovative translational clinician, whose creativity and spirit lit up so many meetings and discussions. None more so than our personal ritual of drinking a bottle of Paul Draper Ridge Zinfandel over dinner on the first evening of the American Society of Haematology meeting, regardless of the time in the UK! David was an adventurous scientist who was fascinated by the biology of leukaemia and had the vision to see that advances in basic science were of immediate potential relevance to patient care. He possessed a rare pragmatism and humility immediately recognising that if scientific advances were to be integrated into day to day patient management, scientists such as himself needed to roll their sleeves up and interact on a daily basis with 'coalface' clinicians across the UK. I well remember shared summer holidays in Burgundy where in the middle of a languorous lunch David would suddenly disappear to e-mail clinicians and research nurses with the latest MRD data on their patients, only to return a couple of hours later to finish the bottle! David was such a fantastic example of how to break down the all too common barriers between the laboratory and the clinic, and his meticulous attention to detail, infectious spirit of enquiry, and commitment to innovation are a lasting inspiration of what can be achieved to improve patient outcome from a genuine multidisciplinary approach.

'A cold coming we had of it': The Journey of the Magi

In 1960 when the British Society of Haematology was established AML was an almost universally incurable disease. Hayhoe and Whitby's¹ seminal paper reported a median survival of 4 months in adults with AML. In the 1970s and 1980s the work of British haematologists notably Frank Hayhoe, Barbara Bain, David Galton, Daniel Catovsky and David Swirsky played a centrally important role in the development of accurate morphological classification of AML, allowing reproducible and accurate diagnosis and confident differentiation from acute lymphoblastic leukaemia and other clinical entities. Subsequently, and working with American and European colleagues, Daniel Catovsky and David Galton played a leading role in the development of the morphological French-American-British (FAB) classification of AML, which for the first time provided agreed and consistent diagnostic criteria at the same time as demonstrating the power of international collaboration.² The extent to which this work transformed the routine diagnosis and treatment of AML should not be under-estimated and I well remember as a Registrar at the Hammersmith Hospital in the 1980s the hushed, almost mystical, reverence with which David Swirsky

would apply and interpret the results of Sudan Black, myeloperoxidase and dual esterase stains on a newly diagnosed patient with acute leukaemia, whilst deftly sweeping away ash that had fallen onto the microscope slide from the ubiquitous cigarette on his lips. No burdensome Health and Safety regulations then!

'The fault dear Brutus is not in our stars but in ourselves': Julius Caesar

The next major advance in the diagnosis and management of AML was the demonstration by David Grimwade, Tony Goldstone and Alan Burnett that karyotypic abnormalities were of important prognostic significance in newly diagnosed adults treated with intensive chemotherapy.³ The Medical Research Council (MRC) classification, as its soubriquet became, was adopted by other international groups as a pre-defined stratification in clinical trials and rapidly impacted clinical practice particularly with regard to which patients should be considered for an allograft. Subsequently the MRC group, in studies led by Panos Kottaridis, Rosemary Gale and David Linch, were among the first to demonstrate the prognostic significance of *fms*-related tyrosine kinase 3 (*FLT3*) gene mutations in newly diagnosed AML; work that transformed risk stratification of fit adults with AML and contributed to the subsequent development of trials of *FLT3* inhibitors as a therapeutic strategy.^{4,5} Next Eli Papaemmanuil and Peter Campbell from the Sanger Institute at Cambridge University, working with Hartmut Dohner and the AMLSG German Co-operative Group, utilised next-generation sequencing (NGS) technology to establish a novel genomically based classification of AML, with the potential to further refine disease prognostication.⁶ This important work is now being extended by Brian Huntly, Pares Vyas and Nigel Russell using UK National Cancer Research Institute (NCRI) trials cohorts. In subsequent work Lynn Quek and Pares Vyas, working with the Birmingham Transplant group, were amongst the first to report the ability of a NGS strategy to predict outcome after allo-SCT in adults with AML.⁷

Inspired by Alan Burnett, David Grimwade and Sylvie Freeman played a key role in the establishment of polymerase chain reaction-based and flow cytometric MRD quantitation to inform risk stratification and guide decision-making in AML. David pioneered the use of serial quantitation of promyelocytic leukaemia:retinoic acid receptor alpha (*PML: RARA*) transcripts in acute promyelocytic leukaemia (APML), as an effective strategy to both identify high-risk patients early during their treatment course and detect early molecular relapse permitting institution of salvage therapies.⁸ In a subsequent pivotal paper he extended this principle to non-APML disease showing that serial quantitation of nucleophosmin 1 (*NPM1*) transcripts in the peripheral blood of adults with *NPM1* + AML treated with induction chemotherapy (IC) was able to identify patients at a high risk of relapse; data that underpins the current practice of

recommending an allograft rather than further chemotherapy in these patients.⁹ In important complementary studies, Sylvie Freeman showed that immunophenotypic quantitation of MRD permitted risk stratification in the great majority of both younger and older adults treated with IC and was able to use these data to further refine definitions of disease resistance.¹⁰

'To be, or not to be, that is the question' Hamlet

It is beyond the scope of this article to exhaustively review the results of the comprehensive programme of clinical trials delivered by the UK AML Working Party (WP). A summary of the results of the most recent seven trials addressing intensive therapy options in a total of 16 959 patients who participated in a total of 33 249 randomisations from more than 190 hospitals in the UK, Denmark, New Zealand and Ireland has recently been published in this Journal.¹¹ Highlights of recent MRC/NCRI trials included the evaluation of the benefit of adjunctive gemtuzumab ozogamicin (Mylotarg) therapy in newly diagnosed adults with AML.¹² Coupled with data from the Acute Leukemia French Association (ALFA) Group, led by Herve Dombret, these trials demonstrated Mylotarg improved survival in adults with good- and intermediate-risk cytogenetics, but showed no survival benefit in patients with an adverse risk karyotype.^{13,14} The NCRI trials group, having demonstrated decreased survival in patients with a *FLT3* mutation were one of the first groups to evaluate the addition of a *FLT3* inhibitor to induction chemotherapy in patients with *FLT3* + AML. Although addition of lestaurtinib to IC did not improve survival, Steve Knapper was able to demonstrate, in a highly effective collaboration, with Mark Levis from John Hopkins that a subgroup of patients who achieved drug levels sufficient to inhibit *FLT3* function *in vitro* demonstrated improved survival.¹⁵ Working as an effective clinical and translational team Alan Burnett, Nigel Russell and David Grimwade also drove fundamental changes in the management of APML. In addition to establishing the clinical value of sequential monitoring of PML-RARA transcripts as a reproducible MRD strategy, the results of the AML17 trial played an important role in establishing all-*trans* retinoic acid (ATRA) and arsenic trioxide as first-line therapy for adults with APML.¹⁶

'We are such stuff as dreams are made on, and our little life is rounded with a sleep.' The Tempest

Most adults with newly diagnosed AML are not fit enough for intensive treatment. The UK AML WP was a trail-blazer in the development of randomised trials in this important and clinically challenging patient population. The AML 14 trial, for the first time, established low dose cytosine arabinoside (ara C) as standard of care in older patients unfit for

IC.¹⁷ Building on the success of AML14, Alan Burnett and Robert Hills went on to pioneer an innovative Pick-A-Winner multi-arm multistage trial design, which allowed simultaneous randomised comparisons of promising new therapies using low-dose ara-C as the standard arm.¹⁸ Reasoning that a significant increase in the complete remission (CR) rate was necessary, although not sufficient, for an agent to improve overall survival the Pick-A-Winner model employed a two-stage evaluation of novel agents requiring a doubling in CR rate before extending the randomisation to look for a survival benefit. Now led by Mike Dennis the LI-1 trial represents not only the largest prospective cohort of patients treated with low dose ara-C, but has also proved an effective strategy for the evaluation of novel therapies that has been applied to other disease settings.

A notable characteristic of the portfolio of prospective randomised trials delivered by the MRC and NCRI groups has been their highly innovative statistical design. Brilliant statisticians, notably Keith Wheatley and Robert Hills, have been at the heart of the development of new trial models, such as the use of factorial design that allows a number of questions to be asked at different stages of the treatment journey, platform trials in which eligibility for randomisation is based on patient and disease including response to prior therapy, the concept of donor-*versus*-no donor analysis to evaluate the benefit of a sibling allograft and the development of the Pick-A-Winner design in older patients.

'If tis well done tis well t'were done quickly' Macbeth

In the 1970s and 1980s UK transplant centres working with the European Society for Blood and Marrow Transplantation (EBMT) and USA colleagues pioneered the development of allo-SCT as an effective strategy to reduce relapse in high-risk acute leukaemia, consequent upon both the augmented anti-tumour activity of a myeloablative conditioning (MAC) regimen and the genesis of a potent graft-*versus*-leukaemia (GVL) effect. The challenge next lay in establishing whether a myeloablative allograft improved overall survival in patients with AML in CR1 transplanted using a sibling donor? The work of Richard Grey and Keith Wheatley in developing the concept of a donor *versus* no donor analysis therefore represented an important advance.¹⁹ Although likely under-estimating the benefit of an allograft, this statistical approach was central to the demonstration in a meta-analysis co-ordinated by Jan Cornelissen and Bob Lowenberg from the HOVON Group, of a survival benefit in the donor group; a benefit that was notably restricted to patients aged <35 years because of the toxicity of a MAC regimen.²⁰ At about this time reduced intensity conditioning (RIC) regimens had been shown to permit the extension, in principle at least, of a potentially curative GVL effect to older patients with high-risk AML. However, these early RIC regimens were associated with a high risk of acute and chronic graft-*versus*-host disease (GVHD). Thus

Steve Mackinnon's development of a RIC regimen incorporating T-cell depletion utilising *in vivo* alemtuzumab represented an important advance permitting allografts to be performed in patients with high-risk AML up to the age of 75 years with only a modest GVHD risk.²¹ Nigel Russell was subsequently able to demonstrate a survival advantage of alemtuzumab-based RIC transplants compared with chemotherapy in older adults with AML.²² In separate studies investigators from the NCRI group working with the EBMT were able to both redefine primary refractory AML and confirm allo-SCT as the only curative therapy in these challenging patients.^{23,24} Recognising that disease relapse is the major cause of treatment failure after a RIC allograft, the prospective examination of novel RIC regimens and post-transplant maintenance strategies, has been led by the NCRI group, in the subsequent FIGARO, COSI and AMADEUS trials.²⁵

'We that are young shall never see so much nor live so long' King Lear

Although outcomes in AML have improved in the last 60 years, particularly in younger patients and those with specific genomically defined subtypes such as APML, the majority of adults remain destined to die of refractory or relapsed disease. However, the investment of trillions pounds and dollars into basic science laboratories over the last six decades, predicated on the delivery of improved clinical outcomes, has at last resulted in the development of a range of novel therapies in both younger and older patients. Drugs such as CPX-351, FLT3 inhibitors, isocitrate dehydrogenase 1 (IDH1) and IDH2 inhibitors and the B-cell leukaemia/lymphoma 2 (Bcl-2) inhibitor venetoclax, coupled with increased accessibility to the curative potential of transplantation promise to significantly improve outcomes in patient subgroups where little progress has previously been made. Coupled with the ability of both genomics and sequential MRD analyses to guide treatment decisions, 2020 is an important time to reappraise the trials infrastructure required if we are to ensure that patients benefit as rapidly as possible from the investment their parents and grandparents have trustingly made into basic science. This will require a radical reconfiguration of how we deliver clinical trials so that we build trial acceleration networks that permit the rapid assessment of an anticipated tsunami of new drug and cellular therapies, so that their path to licensing is hastened. Such trials must be characterised by high levels of academic engagement and embed genomics, MRD and discovery science as key outputs. The Contract Research Organisation sector, which has traditionally been used by the global pharmaceutical sector to deliver licensing trials of novel agents, is palpably failing both the pharmaceutical sector and patients at a time of increased genomic stratification in terms of both speed and cost. At the same time academic co-operative groups, which are ideally placed to deliver trials of the scale required, struggle to obtain funding for investigator initiated trials, particularly after the devastating impact of COVID-19

on the philanthropic sector – and, by relying on a trials infrastructure inherited from the 1990s, are unable to deliver trials with the data quality and pharmacovigilance required by licensing authorities, such as the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA). As a result approval of novel agents is slowed, delaying patient access to breakthrough therapies, and the opportunity for co-operative groups to deliver label informing trials is squandered.

It is therefore increasingly clear that if we are to serve our patients as they deserve in coming years, the development of a new hybrid model of trial delivery will be essential. Co-operative groups, whilst retaining their independence, must now develop the ability to deliver licensing standard clinical trials characterised by the augmented standards of pharmacovigilance and data quality mandated by the FDA and EMA. The value of embedded translational studies addressing mechanism of drug activity and resistance, which are now of increasing importance to the regulatory authorities as demonstrated by Paresch Vyas's and Lynn Quek's insightful work on the mechanism of action of enasidenib in IDH-2 mutated AML, will create added value for this hybrid model.²⁶ Importantly, the income generated by these pivotal licensing studies will create a sustainable funding stream for the delivery of academic investigator trials whose funding is currently under threat. Gratifyingly the UK is playing a leading role in the development of these vitally needed trial delivery models. Building on the visionary work of Bob Lowenberg and the Dutch-Belgian Hematology-Oncology Co-operative Group (HOVON), the UK's Trials Acceleration Programme (TAP) and IMPACT networks have demonstrated how accelerated trial delivery models can transform patient access to novel therapies, whilst at the same time facilitating accelerated drug approval.²⁷ At a time of such therapeutic promise, new and creative models of trial delivery are urgently required; we owe our patients no less.

Acknowledgements

The author would like to acknowledge the support of Cure Leukaemia, Anthony Nolan, NHSBT and Blood Cancer UK for funding of the UK TAP and IMPACT trials networks as well as stimulating discussions with Peter Hillmen, David Marks, Paresch Vyas, Mark Cook, Anjan Thakurta and the inspirational patients Graham Silk and Geoff Thomas.

References

1. Hayhoe FG, Whitby L. The management of acute leukaemia in adults. *Br J Haematol*. 1955;1:1–19.
2. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976;33:451–8.
3. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The

- Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood*. 1998;**92**:2322–33.
4. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood*. 2001;**98**:1752–9.
 5. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med*. 2017;**377**:454–64.
 6. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;**374**:2209–21.
 7. Quek L, Ferguson P, Metzner M, Ahmed I, Kennedy A, Garnett C, Jeffries S, et al. Mutational analysis of disease relapse in patients allografted for acute myeloid leukemia. *Blood Adv*. 2016;**1**:193–204.
 8. Grimwade D, Jovanovic JV, Hills RK, Nugent EA, Patel Y, Flora R, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol*. 2009;**27**:3650–8.
 9. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;**374**:422–33.
 10. Freeman SD, Hills RK, Virgo P, Khan N, Couzens S, Dillon R, et al. Measurable residual disease at induction redefines partial response in acute myeloid leukemia and stratifies outcomes in patients at standard risk without NPM1 mutations. *J Clin Oncol*. 2018;**36**:1486–97.
 11. Burnett AK, Hills RK, Russell N. Twenty five years of UK trials in acute myeloid leukaemia: what have we learned? *Br J Haematol*. 2020;**188**:86–100.
 12. Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol*. 2011;**29**:369–77.
 13. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. 2014;**15**:986–96.
 14. Castaigne S, Pautas C, Terre C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012;**379**:1508–16.
 15. Knapper S, Russell N, Gilkes A, Hills RK, Gale RE, Cavenagh JD, et al. A randomized assessment of adding the kinase inhibitor lestaurtinib to first-line chemotherapy for FLT3-mutated AML. *Blood*. 2017;**129**:1143–54.
 16. Burnett AK, Russell NH, Hills RK, Bowen D, Kell J, Knapper S, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2015;**16**:1295–305.
 17. Burnett AK, Milligan D, Prentice AG, Goldstone AH, McMullin MF, Hills RK, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer*. 2007;**109**:1114–24.
 18. Hills RK, Burnett AK. Applicability of a "Pick a Winner" trial design to acute myeloid leukemia. *Blood*. 2011;**118**:2389–94.
 19. Gray R, Wheatley K. How to avoid bias when comparing bone marrow transplantation with chemotherapy. *Bone Marrow Transplant*. 1991;**7** (Suppl 3):9–12.
 20. Cornelissen JJ, van Putten WLJ, Verdonck LF, Theobald M, Jacky E, Dae-nen SM, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? *Blood*. 2007;**109**:3658–66.
 21. Chakraverty R, Peggs K, Chopra R, Milligan DW, Kottaridis PD, Verfuert S, et al. Limiting transplantation-related mortality following unrelated donor stem cell transplantation by using a nonmyeloablative conditioning regimen. *Blood*. 2002;**99**:1071–8.
 22. Russell NH, Kjeldsen L, Craddock C, Pagliuca A, Yin JA, Clark RE, et al. A comparative assessment of the curative potential of reduced intensity allografts in acute myeloid leukaemia. *Leukemia*. 2015;**29**:1478–84.
 23. Ferguson P, Hills RK, Grech A, Betteridge S, Kjeldsen L, Dennis M, et al. An operational definition of primary refractory acute myeloid leukemia allowing early identification of patients who may benefit from allogeneic stem cell transplantation. *Haematologica*. 2016;**101**:1351–8.
 24. Craddock C, Labopin M, Pillai S, Finke J, Bunjes D, Greinix H, et al. Factors predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukaemia. *Leukemia*. 2011;**25**:808–13.
 25. Goodyear OC, Dennis M, Jilani NY, Loke J, Siddique S, Ryan G, et al. Azacitidine augments expansion of regulatory T cells after allogeneic stem cell transplantation in patients with acute myeloid leukemia (AML). *Blood*. 2012;**119**:3361–9.
 26. Quek L, David MD, Kennedy A, Metzner M, Amatangelo M, Shih A, et al. Clonal heterogeneity of acute myeloid leukemia treated with the IDH2 inhibitor enasidenib. *Nat Med*. 2018;**24**:1167–77.
 27. Fox TA, Horne GA, Craddock C, Cook G, O'Brien S, Fox S, et al. Trial re-investment to build better research for better impact. *Lancet*. 2019;**394**:635–6.